Editorial

Heart failure risk reduction: Is fit and overweight or obese better than unfit and normal weight?

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Heart failure (HF) is a global public health epidemic and burden which is associated with increased morbidity and mortality.(1) The economic burden of HF is also substantial; it has been reported that HF contributes to about $31 billion in annual healthcare expenditure in the USA alone.(2) With the aging of the population and improvements in the treatment of cardiovascular diseases (CVDs), the impact of HF is expected to increase proportionately.(3) In the USA alone, it has been projected that by 2030, 8 million people will be affected by HF.(4)

In addition to other factors, there is a wealth of increasing evidence implicating lifestyle factors such as low physical inactivity, poor cardiorespiratory fitness (CRF), and obesity as established risk factors for HF (**Table**).(5-14) It is well known that higher PA levels are associated with improved health outcomes and better quality of life. CRF is an index of habitual PA levels and is considered the gold standard for aerobic capacity. Several well-designed large-scale epidemiological studies have reported strong, inverse, and graded independent associations of CRF with the risk of HF (**Table**).(8, 11) Similarly, obesity as measured by body mass index (BMI) is related to an increased risk of HF; BMI as a continuous variable is also associated with higher HF risk (**Table**).(5) Other obesity-associated parameters such as waist circumference (WC), waist-to-hip ratio (WHR), body weight, and body fat percentage are also associated with HF risk.(5, 15) There is an inverse relationship between CRF and obesity(16) and given that both low CRF and increased adiposity are each associated with an increased risk of HF, the pathways through which low CRF and obesity might increase the risk of HF are not well understood. The majority of previous studies on higher BMI, other obesity parameters, and HF risk did not account for differences in CRF levels. It has been suggested that a potential mechanism by which obesity parameters such as BMI, WC, and body fat percentage might contribute to the development of HF, is through increased ventricular-arterial stiffness.(17) Recent evidence suggests that CRF may mediate the risk of HF associated with BMI and high CRF may attenuate the deleterious impact of obesity on HF risk.(11, 18) Though high BMI is a risk

factor for HF, there are findings of a “surprising” relationship between BMI and outcomes in HF patients. In patients with already established HF, accumulating evidence suggests that overweight and obese (higher BMI) individuals have substantially improved survival compared to those with normal BMI, a concept which has been termed “reverse epidemiology” or “obesity paradox”.(19) Several mechanisms have been proposed to explain the HF obesity paradox and these include HF therapy being more effective in obese patients(20) and another is the role of CRF; it has been reported that CRF might mitigate or negate the “obesity paradox”.(19, 21) A higher WHR has also been demonstrated to challenge the “obesity paradox”.(22) Indeed, the interplay between obesity, CRF, and HF is not clearly defined and requires further exploration.

There is little knowledge on the association and interaction between CRF, BMI, and incident HF. In this context, Kokkinos and colleagues have conducted an elegant and clinically valuable study that aimed to assess the interactive effect of CRF and BMI on the incidence of HF in US male veterans.(23) The authors utilized a prospective cohort based on a combination of two separate studies with a final sample of 20,254 participants (mean age 58 years). Exercise capacity (peak METs) was used as a measure of CRF from a maximal exercise treadmill test. After a mean follow-up of 14 years, 2,979 HF events were recorded. The association between CRF and incident HF was strong, inverse, graded and was observed regardless of BMI category (normal weight, overweight, and obese). In addition, the association was of similar trend in those <65 and ≥65 years of age, suggesting that CRF is protective of HF regardless of age; though the impact of good CRF on HF risk in the younger participants was more protective. Higher BMI or obesity was associated with an increased HF; however, the association was null on adjustment for CRF. The authors also demonstrated a significant interaction between CRF and BMI levels on HF risk, which increased progressively with decreased CRF within each BMI category.

The strengths of this study include the large sample with adequate numbers of normal weight, overweight, and obese participants; the comprehensive panel of blood-based markers, comorbidities, and lifestyle characteristics which enabled adequate adjustment for potential confounders; and thorough statistical methods which included interaction, dose-response and several sensitivity analyses.(23) The limitations comprised (i) the use of an observational design which is characterised by residual confounding, regression dilution and does not establish causality as acknowledged by the authors; (ii) findings being limited to men and therefore not generalisable to women; (iii) lack of data on physical activity patterns during follow-up, which could have influenced CRF; (iv) absence of data on HF subtypes; and (v) CRF was not assessed using respiratory gas analysis (directly measured oxygen uptake, VO_2), which is a more objective and quantitative assessment of this measure. In our previous studies (**Table**), we have utilized directly assessed maximal VO_2 as the measure of CRF, which considers body weight (ml/kg/minute); whereas indirectly assessed CRF (treadmill time or exercise test watts) does not.

The current findings of Kokkinos and colleagues are very relevant and welcome, as they have several clinical implications for HF prevention.(23) The findings of an independent, inverse, and graded association between CRF and HF risk are consistent with previous work in this area.(8, 11) Furthermore, the association persisted despite levels of BMI. The association of obesity with HF was attenuated on accounting for CRF level. Overall, these findings suggest the association between obesity and HF may be explained by low CRF and that high fitness levels could counteract the adverse effects of obesity on HF. It appears increased CRF, as an indicator of cardiovascular function, rather than normal weight protects against HF risk and as the authors have reported, the findings lend support to the concept that fit and overweight or obese is better than unfit and normal weight in HF prevention. Given the adverse effect of aging on the incidence of HF, the finding of a protective effect of high CRF on HF risk regardless of age is very positive news. In recent years, the assessment of CRF has achieved significant clinical merit and is a vital part of

CVD risk assessment. Cardiopulmonary exercise testing (CPX), which includes the assessment of peak VO_2 (a measure of CRF) and markers of ventilatory efficiency, is a clinically useful tool in HF risk assessment.

CRF is influenced by both genetic as well as environmental factors; approximately half of the variation in CRF has been attributed to heritable factors, with the contribution of inherited factors to the response of CRF to PA approximating 45-50%.(24) It also depends on several factors such as baseline health and fitness status, type, duration, and intensity of PA. The level of CRF is also an indicator a chain of multiple physiological processes that include: pulmonary ventilation and vascular function, right and left ventricular (LV) function, the capacity of the vasculature to accommodate and efficiently transport blood from the heart to other organs matching their oxygen requirements, the ability of the muscle cells to use the oxygen and other essential nutrients delivered by the blood, and the ability to activate all necessary muscle fibres needed for body movement. Left ventricular stroke volume, maximal heart rate, and arteriovenous oxygen difference at exercise have essentially determined CRF level. Left ventricular function is a key measure of HF and CRF level may reflect LV function. As CRF is related to the integration of human body function under physiological stress conditions, it can be employed as a very useful indicator of the risk for HF, reflecting whole body functional status among patients with existing HF.

We applaud the efforts of Kokkinos and colleagues for throwing more light on the interplay between CRF, obesity, and HF. The strong inverse, graded, and consistent observational association between CRF and future HF risk suggests a causal association; however, this needs to be demonstrated in robust intervention studies. Conclusive evidence from intervention studies linking an increased PA level with improved CRF to decreased HF incidence is lacking. Mendelian randomisation studies of genetic variants related to CRF may provide another route to assess causality. The health benefits associated with regular PA, which includes aerobic and strength training components, cannot be overemphasized.

Even the least active behavior which is standing (rather than sitting) is reported to be associated with health benefits.(25) In the absence of further studies, encouraging good CRF via regular PA should be promoted extensively via population wide approaches. Healthcare providers should also include CRF improvement in treatment of patients with chronic diseases and at high risk in clinical practice. Despite the recommendations to promote and maintain PA among the general population and individuals at high risk of HF, there are still some unanswered questions. The optimal PA or exercise training programme for HF prevention is uncertain. Studies are warranted to compare the cardiovascular responses to different PA types and their frequencies, intensities and durations in different populations such as the elderly and those at elevated HF risk. In the absence of these studies, the 2018 Physical Activity Guidelines Advisory Committee Scientific Report recommends 150-300 min/week of moderate-intensity or 75-150 min/week of vigorous-intensity aerobic PA/ exercise for adults, as this is associated with substantial health benefits in most people.(26)

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Table 2. Individual studies and meta-analyses of prospective studies of physical activity, cardiorespiratory fitness, and body mass index with heart failure

Author, year of publication [reference]	Name of study or source of participants	Exposure type	No. of participants (number of studies*)	No. of HF cases	Combined risk (95% CI)	Risk comparison reported
Body mass index						
Aune, 2016 [5]	Meta-analysis	BMI	647,388 (23)	>15,905 incident cases	1.41 (1.34-1.47)	Per 5-unit increment in BMI
Aune, 2016 [5]	Meta-analysis	BMI	215,657 (4)	1,015 deaths	1.25 (0.85-1.87)	Per 5-unit increment in BMI
Physical activity						
Pandey, 2015 [6]	Meta-analysis	PA	370,460 (12)	20,203	0.70 (0.7-0.73)	Highest versus lowest PA level
Echouffo-Tcheugui, 2015 [7]	Meta-analysis	PA	165,695 (10)	NR	0.72 (0.67-0.79)	Most versus least physically active
Cardiorespiratory fitness						
Khan, 2014 [8]	KIHD	VO_2max	1873	152	0.81 (0.69-0.95)	Per 1 MET increase
Andersen, 2015 [9]	Swedish Military Service Conscription Registry	Maximal exercise capacity (Watts)	1,126,899	3,949	0.60 (0.53-0.67)	Per extreme quintiles
Khan, 2017 [10]	KIHD	VO_2max	2,089	522	0.85 (0.78-0.93)	Per 1 MET increase
Myers, 2017 [11]	VETS	Exercise capacity (in METs)	21,080	1,902	0.25 (0.21-0.31)	High-fit versus least-fit
Kupsky, 2017 [12]	Henry Ford Health Systems	Workload (in METs)	66,329	4,652	0.84 (0.82-0.86)	Per 1 MET increase
Lindgren, 2017 [13]	Swedish Military Service Conscription Registry	Maximum work capacity/weight	1,226,623	7,656	1.58 (1.36-1.84)	Low versus high CRF
Khan, 2018 [14]	KIHD	VO_2max	481	46	0.76 (0.59-0.99)	Per 1 MET change in CRF

*, for meta-analysis; BMI, body mass index; CCLS, Cooper Center Longitudinal Study; CRF, cardiorespiratory fitness; HF, heart failure; KIHD, Kuopio Ischemic Heart Disease; MET, metabolic equivalent; NR, not reported; PA, physical activity; VETS, Veterans Exercise Testing Study; VO_2max, maximal oxygen uptake